

PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Improvements relating to Halogen Substituted Diphenyl Urea and Thiourea Compounds and their use

We, J. R. GEIGY A.—G., a body corporate organised according to the laws of Switzerland, of 215 Schwarzwaldallee, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention concerns the production of polyhalogen substituted monohydroxydiphenyl urea and thiourea compounds which have at least one halogen substituent in each of the two benzene rings but no acid water solubilising groups. It also concerns their use as disinfectants.

o-Hydroxydiphenyl urea and thiourea compounds which have at least one halogen substituent in each of the two benzene rings but no acid water solubilising groups, are new. They can be produced by methods known *per se* by reacting halogen substituted *o*-hydroxyaminobenzene compounds with a compound introducing a halogen phenyl carbamyl- or thiocarbamyl radical into the primary amino group. Chiefly the halogen substituted phenyl isocyanates and/or phenyl mustard oils can be used as compounds which introduce the halogen phenyl carbamyl or thiocarbamyl radical. Phenyl carbamic acid phenol esters which are easily obtained from chloroformic acid phenol esters and halogen aminobenzenes can also be used as starting materials in the process according to the present invention, as, at even moderate temperatures with correspondingly chosen halogen-*o*-hydroxyaminobenzene compounds, they produce *o*-hydroxydiphenyl ureas according to the present invention whilst splitting off phenol. Also the reaction of suitably substituted phenyl ureido compounds with *o*-aminohydroxybenzene compounds chosen according to this invention leads, in individual cases, to polyhalogen substituted *o*-hydroxydiphenyl ureas. Finally, also the use of halogen benzoylazides, which under the conditions of

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the reaction known *per se* transform themselves whilst splitting off nitrogen into the corresponding halogen phenyl isocyanates, falls within the scope of the present invention. However, the addition of halogen phenyl isocyanate or halogen phenyl mustard oil to suitably substituted halogen-*o*-aminobenzene compounds is to be preferred to all other methods.

Examples of phenyl isocyanates or phenyl mustard oils which can be used in the process according to the present invention are: 4-chlorophenyl isocyanate, 3,4-dichlorophenyl isocyanate, 3-trifluoromethyl-4-chlorophenyl isocyanate, 4-bromophenyl isocyanate, 4-fluorophenyl isocyanate, 3,4-dibromophenyl isocyanate, 3,4,5-trichlorophenyl isocyanate, 2,3,4-trichlorophenyl isocyanate, 4-fluoro-3-chlorophenyl isocyanate, 4-chlorophenyl mustard oil, 3,4-dichlorophenyl mustard oil, 3-trifluoromethyl-4-chlorophenyl mustard oil. They are reacted according to the invention with halogen substituted *o*-aminophenols. Examples of such are: 4-chloro-2-amino-1-hydroxybenzene, 5-chloro-2-amino-1-hydroxybenzene, 4,5-dichloro-2-amino-1-hydroxybenzene, 3,4,6-trichloro-2-amino-1-hydroxybenzene, 4- or 5-bromo-2-amino-1-hydroxybenzene, 4,6-dibromo- or 4,6-dichloro-2-amino-1-hydroxybenzene, 4,5-dibromo-2-amino-1-hydroxybenzene, 4-chloro-5-trifluoromethyl-2-amino-1-hydroxybenzene, 4-chloro-5-bromo-2-aminophenyl.

Phenyl carbamic acid phenol esters usable in the process according to the present invention are: 3,4-dichlorophenyl carbamic acid phenol ester or *o*-cresyl ester, 3-trifluoromethyl-4-chlorophenyl carbamic acid phenol or *o*-cresyl ester, 4-bromophenyl carbamic acid phenol ester, 4-fluorophenyl carbamic acid phenol ester 3,4-dibromophenyl carbamic acid phenol ester.

According to the present invention the com-

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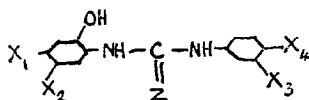
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ponents are so chosen that there is at least one halogen substituent in each benzene ring in the new 2-hydroxydiphenyl urea or thiourea compounds whereby in the benzene ring containing no hydroxyl group, the halogen substituent can be replaced by the trifluoromethyl group.

It is preferable that these halogen substituents occupy the *p*- and also, if desired, the *m*-position to the urea or thiourea bridge. Halogen substitution in pairs in the *m*- and *p*-positions to the ureido group in at least one of the benzene rings is particularly advantageous. If desired, alkyl or alkoxy groups can be present as further substituents, e.g. a methyl group in either the *m*- or *p*-position to the hydroxyl group or in the *o*-position to the urea bridge in the benzene ring containing no hydroxyl group.

Particularly valuable *o*-hydroxydiphenyl ureas according to this invention correspond to the general formula:



wherein X_1 to X_4 represent halogen or hydrogen,

X_5 in addition may represent the trifluoromethyl group whilst not more than one of the four symbols X represents hydrogen, and

Z represents an oxygen or a sulphur atom, and wherein the two benzene rings can each contain a further substituent, e.g. another halogen or a methyl group.

Some of the polyhalogen substituted *o*-hydroxydiphenyl urea or thiourea compounds, with suitable halogen substitution, have a very good bactericidal action. In particular they are very active against the bacterial flora which cause perspiration odours and they are, for this reason and because of their low toxicity, very suitable for use as deodorants in laundering, and for human use when incorporated in cleansing agents such as soaps or shampoos, or as additives to cosmetic agents such as ointments or creams.

The following examples illustrate the invention without limiting it in any way. Where not otherwise stated, parts are given as parts by weight and the temperatures are in degrees Centigrade. The relationship of parts by weight to parts by volume is as that of kilograms to litres.

EXAMPLE 1.

A hot solution of 21.5 parts of 3,4-dichlorobenzoic acid azide in 50 parts by volume of toluene is added to a hot solution of 14.5 parts of 5-chloro-2-aminophenol in 250 parts by volume of toluene. After boiling for 15 minutes and then cooling the mixture, the N-3,4-dichlorophenyl-N¹.2¹-hydroxy - 4¹ - chloro -

phenyl urea formed is filtered off. When recrystallised from diluted alcohol, it melts at 201—202°. This compound also has desirable fungicidal properties.

EXAMPLE 2.

A mixture of 22.5 parts of 3,4-dichlorophenyl urea, 14 parts of 2-amino-4-chlorophenol and 40 parts by volume of glacial acetic acid is boiled until no more 2-amino-4-chlorophenol can be traced. The cooled mass is diluted with a little water whereupon it solidifies. The precipitate is filtered off and extracted with diluted caustic soda to remove the 5-chlorobenzoxazolone formed. The residue is dissolved in 15% alcohol with the addition of caustic soda lye, undissolved particles are filtered off and the N-3,4-dichlorophenyl-N¹.2¹-hydroxy-5¹-chlorophenyl urea is precipitated with acetic acid. After recrystallising from dioxane it melts at 205—206°.

EXAMPLE 3.

31 Parts of 3,4-dichlorophenyl carbamic acid phenyl ester and 17 parts of 2-amino-4,5-dichlorophenol are dissolved in 100 parts by volume of dioxane and 50 parts of a 40% sodium acetate solution are added. The mixture is stirred at 90—95° until for practical purposes no more 2-amino-4,5-dichlorophenol can be traced, which is for about half an hour. N-3,4-dichlorophenyl - N¹.2¹ - hydroxy-4¹.5¹-dichlorophenyl urea which has partly precipitated during the reaction is filtered off after cooling and recrystallised from tetrachloroethane. It melts at 201—202°.

EXAMPLE 4.

18 Parts of 2-amino-4,5-dichlorophenol are dissolved in 25 parts by volume of acetone and a solution of 17 parts of 4-chlorophenyl mustard oil in 25 parts by volume of acetone is added. The whole is stirred for 3 hours at 35°, diluted with water and the N-4-chlorophenyl - N¹.2¹ - hydroxy - 4¹.5¹ - dichlorophenyl thiourea which precipitates is filtered off. After recrystallising from benzene it melts at 146—147° on decomposition.

EXAMPLE 5.

A solution of 10 parts of 3,4-dichlorophenyl mustard oil in 40 parts by volume of benzene is added to a solution of 10 parts of 2-amino-4,5-dichlorophenol in 20 parts by volume of acetone. After stirring for 3 hours, the product is precipitated with petroleum ether and the separated N-3,4-dichlorophenyl - N¹.2¹ - hydroxy - 4¹.5¹ - dichlorophenyl thiourea is recrystallised from benzene. M.P. 159—160° on decomposition.

EXAMPLE 6.

100 Parts of an 18% solution of 3,4-dichlorophenyl isocyanate in nitrobenzene are added at 30—35° while cooling to a solution

of 19 parts of 2-amino-5-bromophenol in 25 parts by volume of acetone. The whole is stirred for an hour, filtered, the product is washed with benzene and recrystallised from diluted alcohol. The N-3,4-dichlorophenyl-N¹.2¹-hydroxy-4¹-bromophenyl urea obtained melts at 198—199°.

EXAMPLE 7.

100 Parts of an 18% solution of 3,4-dichlorophenyl isocyanate in nitrobenzene are poured at 30—35° into a solution of 23 parts of 2-amino-4-chloro-5-bromophenol in 40 parts by volume of acetone and the whole is stirred for 1 hour. The N-3,4-dichlorophenyl-N¹.2¹-hydroxy-4¹-bromo-5¹-chlorophenyl urea is filtered off, boiled with benzene to remove the nitrobenzene, again filtered off and recrystallised from diluted alcohol. M.P. 201—202° on decomposition.

EXAMPLE 8.

111 Parts of a 9% solution of 3-trifluoromethyl-4-chlorophenyl isocyanate in chlorobenzene is poured at 30° into a solution of 9 parts of 2-amino-4,5-dichlorophenol in 25 parts by volume of acetone. After stirring for 2 hours, the product is filtered off and recrystallised from benzene. N-3-trifluoromethyl-4-chlorophenyl-N¹.2¹-hydroxy-4¹.5¹-dichlorophenyl urea melts at 174—175°.

EXAMPLE 9.

123 Parts of a 9% solution of 3-trifluoromethyl-4-chlorophenyl isocyanate are poured at 30—35° into a solution of 11 parts of 3,4,6-trichloro-2-aminophenol in 50 parts by volume of acetone. On completion of the reaction, the N-3-trifluoromethyl-4-chlorophenyl-N¹.2¹-hydroxy-3¹.5¹.6¹-trichlorophenyl urea formed is filtered off and recrystallised from diluted alcohol. M.P. 198—199°.

EXAMPLE 10.

8 parts of 2-amino-4,6-dichlorophenyl are dissolved in 70 parts by volume of acetone and the solution is poured at room temperature into

8 parts of 2,3,4-trichlorophenyl isocyanate in 30 parts by volume of acetone. After stirring for 2 hours, the product is filtered off. Recrystallised from glacial acetic acid, N-2,3,4-trichlorophenyl-N¹.2¹-hydroxy-3¹.5¹-dichlorophenyl urea melts at 214—215°.

EXAMPLE 11.

100 Parts of an 18% solution of 3,4-dichlorophenyl isocyanate in nitrobenzene are added at 30° to a solution of 22 parts of 2-amino-4,5,6-trichlorophenol in 50 parts by volume of acetone. After stirring for one hour, the N-3,4-dichlorophenyl-N¹.2¹-hydroxy-3¹.4¹.5¹-trichlorophenyl urea is precipitated with petroleum ether, filtered off and recrystallised from chlorobenzene. M.P. 210—211° on decomposition.

The bactericidal properties and the melting points of some diphenyl urea or thiourea compounds according to this invention can be seen from the following Table, that gives particulars from which said compounds can be identified. The bactericidal properties were determined on *Staphylococcus aureus* as follows:

A standard suspension, which is prepared by adding sterilised tap water to the germs of 16 hour agar cultures, the density of which is brought to 85% transparency in the so-called BIO-PHOTO-COL-apparatus according to Hellige, is mixed with graduated dilutions of the disinfectant to be tested (in aqueous solution). Duration of test: 10 minutes, temperature: 20°.

At the end of the 10 minutes, 2 sub-cultures from each reaction mixture are prepared with a glucose broth. The sub-cultures are bred at 37° C. After 48 hours, the development of sterility of the sub-cultures is determined. The bactericidal activity of a disinfectant is determined by the minimum concentration required to kill, with certainty, a standard suspension of test germs under certain conditions. The minimum concentration having a bactericidal action is ascertained by graduated concentrations according to the dilution process principle and is expressed in 10⁻⁶ mol.

TABLE

Ureas

No.	<i>o</i> -aminophenol	phenyl	M.P.	minimum bactericidal concentration expressed in 10^{-6} mol
1.			206—207°	25
2.			201—202°	12.5
3.			198—199°	25
4.			204—205°	25
5.			201—202° on decomposition	12.5
6.			174—175°	6.2
7.			201—202°	3.1
8.			214—215°	12.5
9.			198—199°	6.2

No.	<i>o</i> -aminophenol	phenyl	M.P.	minimum bactericidal concentration expressed in 10^{-6} mol
10.			210—211° on decomposition	3.1
11.		Thioureas: 	146—147° on decomposition	12.5
12.			159—160° on decomposition	12.5

EXAMPLE 12.

5 99 Parts of soap flakes and 1 part of N-3,4-dichlorophenyl - N¹.2¹ - hydroxy - 4¹.5¹ - dichlorophenyl urea together with a little perfume are well mixed either direct or dissolved in a little alcohol in a mixing apparatus. The finished mixture is refined by rolling and then pressed into tablet form. A toilet soap having a deodorant action is thus obtained.

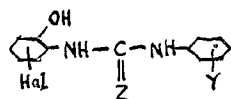
10 A similar good action is obtained if 97 parts of soap flakes and 3 parts of N-3,4-dichlorophenyl - N¹.2¹ - hydroxy - 3¹.4¹.5¹-trichlorophenyl urea are used as starting materials.

EXAMPLE 13.

15 A 1% aqueous solution of a cleansing agent which contains 10 parts of one of the diphenyl ureas named in example 12 and 90 parts of a non-ionogenic or anion active synthetic washing agent, produces a washing liquor which is suitable for example for the cleansing of household or personal linen.

What we claim is:—

25 1. A polyhalogen substituted compound having the general formula:

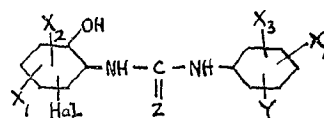


wherein Hal represents halogen,

Y represents halogen or the trifluoromethyl group, and

30 Z represents an oxygen or sulphur atom; and the two benzene rings may contain further substituents but no water solubilising groups.

2. A polyhalogen substituted compound having the formula:

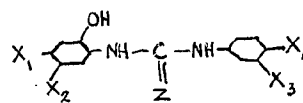


wherein X₁, X₂, X₃ and X₄ represent hydrogen or halogen,

Y represents halogen or the trifluoromethyl group, and

Z represents an oxygen or sulphur atom.

3. A polyhalogen substituted compound having the formula:



wherein X₁, X₂, X₃ and X₄ represent halogen or hydrogen,

X₃ may also represent the trifluoromethyl group whilst not more than one of the four symbols X represents hydrogen, and

Z represents an oxygen or a sulphur atom.

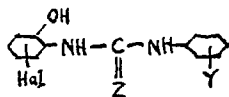
4. Process for the production of polyhalogen substituted monohydroxydiphenyl urea or thiourea compounds, the benzene rings of which contain no acid water solubilising groups, characterised by reacting halogen substituted *o*-hydroxyaminobenzene compounds with a compound which introduces a halogen or trifluoromethyl substituted phenyl carbamyl or thiocarbamyl radical into the primary amino group.

5. Manufacture of polyhalogen substituted compounds substantially as herein described

with reference to any of the foregoing examples 1 to 11.

5 6. A polyhalogen substituted compound as hereinbefore identified by or in any of the examples 1 to 11 or by the Table.

7. Germicidal agent characterised by a content of a compound of the general formula:



10 wherein Hal represents halogen,
Y represents halogen or the trifluoromethyl group,

Z represents an oxygen or a sulphur atom, and the two benzene rings may contain further substituents but no water solubilising groups.

8. A process of forming a toilet soap containing a polyhalogen substituted compound, substantially as described in Example 12. 15

9. A process of producing a liquor suitable for cleansing household or personal linen and containing a polyhalogen substituted compound, substantially as described in Example 13. 20

For the Applicants,
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